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Visfatin in human pregnancy: maternal gestational diabetes *vis-à-vis* neonatal birthweight

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Abstract

Objective: Adipose tissue dysfunction, characterized by dysregulation of adipokines production and/or secretion, has been implicated in the pathophysiology of type-2 diabetes mellitus, a metabolic complication closely related to gestational diabetes mellitus (GDM). Recently, an association between circulating maternal visfatin, a novel adipokine with metabolic and immunoregulatory properties, and impaired glucose metabolism as well as with altered fetal growth, has been proposed. The aims of this study were to determine whether there is an association between maternal plasma visfatin concentration, GDM, and a large-for-gestational-age (LGA) newborn.

Study design: This cross-sectional study, included pregnant women at term in the following groups: 1) normal pregnancy and an appropriate-for-gestational-age (AGA) neonate (n = 54); 2) normal pregnancy and an LGA newborn (n = 47); 3) GDM and an AGA newborn (n = 56); 4) GDM and an LGA newborn (n = 45). The study population was further stratified by first trimester BMI (< 25 vs. ≥ 25 kg/m^2). Maternal plasma visfatin concentration was determined by ELISA. Parametric and non-parametric statistics were used for analysis.

Results: 1) Among women who delivered an AGA neonate, the median maternal plasma concentration of visfatin was higher in patients with GDM than in those with a normal pregnancy; 2) Among women with a normal pregnancy, those who delivered an LGA neonate had a higher median maternal plasma visfatin concentration than those who delivered an AGA neonate; 3) among patients with normal BMI, there were no significant differences in the median maternal plasma visfatin concentration between the four study groups; and 4) maternal GDM, as well as delivery of an LGA neonate were independently associated with a higher maternal plasma visfatin concentrations.

Conclusion: The linkage between increased maternal circulating visfatin and the presence of GDM or delivery of an LGA neonate supports the hypothesis that perturbation of adipokines homeostasis may play a role in the pathophysiology of GDM or excess fetal growth.

Keywords: adipokine; adipose tissue; appropriate-for-gestational-age (AGA); gestational diabetes mellitus (GDM); large-for-gestational-age (LGA); pre-B cell colony-enhancing factor (PBEF); visfatin.

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Introduction

Pregnancy is a unique condition characterized by transient physiologic insulin resistance [21, 24, 25, 30–32, 58, 65, 105, 109, 114, 158, 167, 177] which progresses with advancing gestation and approaches that of non-pregnant patients with type-2 diabetes mellitus (DM) [18]. Teleologically, this physiological adaptation is aimed to facilitate delivery of nutrients to the fetus [104, 165]. The implicit paradigm that has been governed the understanding of the metabolic adaptation during pregnancy, was that insulin resistance should be attributed to the "diabetogenic" effect of placental hormones, such as human placental lactogen (hPL), estrogen, and progesterone. Indeed, both *in vivo* and *in vitro* studies support this view [11, 13, 41, 90, 91, 159, 166, 169]. However, during the last decade, with the recognition of adipose tissue as an active endocrine organ, an alternative paradigm for the pathogenesis of insulin resistance has emerged [12, 51, 77, 78, 155, 186, 190]. Indeed, a solid body of evidence supports the central role of adipose tissue in the regulation of energy homeostasis as well as

in metabolism and inflammation in pregnant and non-pregnant subjects [8, 9, 28, 51, 68, 83, 88, 89, 93, 99, 118, 126, 128, 136, 162–164, 178, 185, 187, 194].

Visfatin is a 52 kDa adipokine, which is preferentially produced by visceral adipose tissue [63, 82, 174] and corresponds to the previously identified growth factor for early B cell, termed pre-B cell colony-enhancing factor (PBEF) [86, 124, 149, 170, 198]. Recently, the metabolic effects of visfatin have been highlighted. Indeed, *in vitro*, adipocytes exposure to glucose increased their secretion of this adipokine [73]. Moreover, visfatin exerts insulin-like activity as a growth factor for osteoblasts [195]. Plasma concentrations of visfatin are higher in patients with type-2 DM [36, 53, 116, 171] as well as in obesity [19, 35, 55, 56, 72, 87, 171, 203] than in normal subjects, and have a positive correlation with body mass index (BMI) [19, 35, 113, 171] and waist-to-hip ratio [36]. Collectively, these data suggest that visfatin has a role in the physiology and pathophysiology of glucose metabolism.

Only a handful of studies have addressed the maternal concentration of visfatin in human pregnancy [34, 50, 52, 71, 101, 112, 120, 121, 125]. Furthermore, data regarding circulating maternal concentrations of visfatin in patients with gestational diabetes mellitus (GDM) are both scarce and conflicting. Indeed, maternal visfatin concentrations (plasma/serum) were reported to be higher [101, 112] and lower [34, 71] in patients with GDM than in normal pregnant women. Interestingly, maternal plasma concentrations of visfatin are significantly elevated in patients with fetal growth restriction than in those with an appropriate-for-gestational-age (AGA) neonate. Thus, the aims of this study were to determine whether there is an association between maternal plasma visfatin concentration, GDM, and a large-for-gestational-age (LGA) newborn.

Materials and methods

A cross-sectional study was conducted by searching our clinical database and bank of biological samples, and included pregnant women at term in the following groups: 1) normal pregnant women who delivered an AGA newborn (n = 54); 2) normal pregnant women who delivered an LGA newborn (n = 47); 3) women with GDM who delivered an AGA newborn (n = 56); and 4) women with GDM who delivered an LGA newborn (n = 45). Women with multiple pregnancies or fetal congenital anomalies were excluded.

All women provided written informed consent prior to the collection of maternal blood samples. The utilization of samples for research purposes was approved by the institutional review boards of Wayne State University, Sotero del Rio Hospital and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD/ NIH/DHHS). Many of these samples have been previously employed to study the biology of inflammation, hemostasis, and growth factor concentrations in normal pregnant women, and those with pregnancy complications.

Definitions

The inclusion criteria for normal pregnancy were: (1) no medical, obstetrical or surgical complications; (2) intact membranes; (3) delivery of a term neonate (>37 weeks) with a birth weight above the 10th percentile; [7] and (4) a normal oral 75-g oral glucose tolerance test (OGTT) between 24–28 weeks of gestation based on World Health Organization (WHO) criteria [3, 6].

All women underwent a 75-g OGTT between 24 and 28 weeks of gestation. Diagnosis of GDM was based on the World Health Organization (WHO) criteria of fasting plasma glucose ≥126 mg/dL (≥7.0 mmol/L) or plasma glucose ≥140 mg/dL (≥7.8 mmol/L) two hours after the 75-g OGTT [3, 6]. GDM patients were treated with diet. LGA newborn was defined as an infant with birth weight above the 90th percentile [7, 69]. The first trimester BMI was calculated according to the following formula: weight (kg)/height (m)^2 and patients were classified according to the definitions of the WHO [2]. A normal weight was defined as BMI between 18.5 and 24.9 kg/m^2 and overweight/obese as BMI ≥25 kg/m^2.

Sample collection

Maternal blood samples were collected at clinical visit. The gestational ages of sample collection were ≥37 weeks for all women included in the study. Blood was centrifuged at 1300×*g* for 10 min at 4°C. The plasma obtained was stored at –80°C until analysis.

Human visfatin C-terminal immunoassay

Concentrations of visfatin in maternal plasma were determined using specific and sensitive enzyme immunoassays purchased from Phoenix Pharmaceuticals, Inc (Belmont, CA, USA). Visfatin C-terminal assays were validated in our laboratory for using human plasma prior to the conduction of this study. Validation included spike and recovery experiments, which produced parallel curves indicating that maternal plasma matrix constituents did not interfere with antigen-antibody binding in this assay system. Visfatin enzyme immunoassays are based on the principle of competitive binding and were conducted according to recommendation of the manufacturer. Briefly, assay plates are precoated with a secondary antibody and the non-specific binding sites have been blocked. Standards and samples were incubated in the assay plates along with primary antiserum and biotinylated peptide. The secondary antibody in the assay plates bound to the Fc fragment of the primary antibody whose Fab fragment competitively bound with both the biotinylated peptide and peptide standard or targeted peptide in the samples. Following incubation, the assay plates were repeatedly washed to remove unbound materials and incubated with a streptavidin-horseradish peroxidase (SA-HRP) solution. Following incubation, unbound enzyme conjugate was removed by repeated washing and a substrate solution was added to the wells of the assay plates and color developed in proportion to the amount of biotinylated peptide-SA-HRP complex but inversely proportional to the amount of peptide in the standard solutions or the samples. Color development was stopped with the addition of an acid solution and the intensity of color was read using a programmable spectrophotometer (SpectraMax M2, Molecular Devices, Sunnyvale, CA, USA). Maternal plasma concentrations of visfatin C were determined by interpolation from individual standard curves composed of human visfatin peptide. The calculated

inter- and intra-assay coefficients of variation for Visfatin C-terminal immunoassays in our laboratory were 5.3% and 2.4%, respectively. The sensitivity was calculated to be 0.04 ng/mL.

Statistical analysis

The Shapiro-Wilk and Kolmogorov-Smirnov tests were used to test for normal distribution of the data. Data are presented as median and interquartile range (IQR). Non-parametric methods were used to perform the statistical analysis for parameters which were not normally distributed and comparisons among groups were performed using the Kruskal-Wallis test with post hoc test by Mann-Whitney *U*-test. Parametric tests were used for analysis of those parameters that were normally distributed and the comparisons among groups were performed using one-way ANOVA with Bonferroni adjustment for the calculated P-value in order to maintain the significance level at 0.05. Multiple linear regression analysis was used to determine which factors were significantly and independently correlated with maternal plasma visfatin concentration (after log transformation). The following parameters were included in the model: maternal age, maternal BMI, gestational age at blood collection, GDM and LGA. The statistical package employed was SPSS 14 (SPSS Inc., Chicago, IL, USA). A P-value of <0.05 was considered statistically significant.

Results

The clinical and demographic characteristics of the study groups are presented in Table 1. Patients with GDM and an AGA neonate ($P=0.01$) or those with GDM and an LGA neonate ($P<0.01$) had a higher median maternal age than normal pregnant women with an AGA neonate.

Maternal plasma visfatin concentration in women with a normal pregnancy

Visfatin was detected in the plasma of all subjects. There was a significant difference in the median maternal plasma visfatin concentration among the groups ($P=0.006$, Kruskal-Wallis).

Among women with a normal pregnancy, those with an LGA neonate had a higher median maternal plasma visfatin concentration than those with an AGA neonate (LGA 19.5 ng/mL, IQR 16.2–22.0 vs. AGA 16.6 ng/mL, IQR 12.2–19.7, $P<0.01$; Figure 1). Among women who delivered an AGA neonate, the median maternal plasma concentration was higher in patients with GDM than those with a normal pregnancy (GDM: 18.3 ng/mL, IQR 15.9–22.0 vs. normal pregnancy 16.6 ng/mL, IQR 12.2–19.7, $P=0.01$; Figure 1).

Maternal plasma visfatin concentration in women with gestational diabetes mellitus

Patients with GDM who delivered an LGA neonate had a higher median maternal plasma visfatin concentration than those with a normal pregnancy and an AGA neonate (GDM + LGA 19.7 ng/mL, IQR 16.2–23.1 vs. normal pregnancy + AGA 16.6 ng/mL, IQR 12.2–19.7, $P<0.01$; Figure 1). There were no significant differences in the median maternal plasma visfatin concentration in women with a normal pregnancy and an LGA neonate and patients with GDM who delivered either an LGA or AGA neonate ($P=0.9$ and $P=0.3$, respectively; Figure 1).

Patients with GDM who delivered an AGA ($P=0.002$) or an LGA neonate ($P<0.001$) had a higher median maternal BMI than those with a normal pregnancy and an AGA neonate. Similarly, patients with GDM and an LGA neonate ($P=0.02$) had a higher median maternal BMI than those with a normal pregnancy and an LGA neonate (Table 1). The rate of overweight/obese women was higher in patients with GDM who delivered an LGA neonate than in those with a normal pregnancy who delivered an AGA neonate ($P=0.03$).

Maternal plasma visfatin concentration in normal and overweight/obese pregnant women with a normal pregnancy

Among overweight/obese women with a normal pregnancy, those with an LGA neonate had a higher median

Table 1 Clinical and demographic characteristics of the study population.

	Normal pregnancy AGA neonate (n = 54)	Normal pregnancy LGA neonate (n = 47)	GDM AGA neonate (n = 56)	GDM LGA neonate (n = 45)
Maternal age (years)*,#	27 (22–30)	28 (22–32)	32 (24–36)	30 (25–35)
BMI (kg/m^2)*,#,§	23 (22–25)	24 (22–28)	26 (22–29)	27 (23–32)
BMI ≥ 25#	17 (31.4%)	21 (44.6%)	36 (64.2%)	30 (66.6%)
Gestational age at blood sampling (weeks)	39 (38–40)	39 (38–40)	38 (38–40)	38 (38–39)
Gestational age at delivery (weeks)	39 (38–40)	39 (38–40)	39 (38–40)	38 (38–39)
Birth weight (g)#,&,$,‡	3390 (3150–3612)	4170 (4050–4415)	3455 (3235–3717)	4190 (4030–4410)

*$P<0.05$ – Normal pregnancy + AGA vs. GDM + AGA, #$P<0.05$ – Normal pregnancy + AGA vs. GDM + LGA, §$P<0.05$ – Normal pregnancy + LGA vs. GDM + LGA, &$P<0.05$ – Normal pregnancy + AGA vs. Normal pregnancy + LGA, $$P<0.05$ – GDM + AGA vs. Normal pregnancy + LGA, ‡$P<0.05$ – GDM + AGA vs. GDM + LGA.

Values are expressed as median (IQR) or as number (percentage); AGA, appropriate for gestational age; LGA, large for gestational age; GDM, gestational diabetes mellitus; BMI, body mass index.

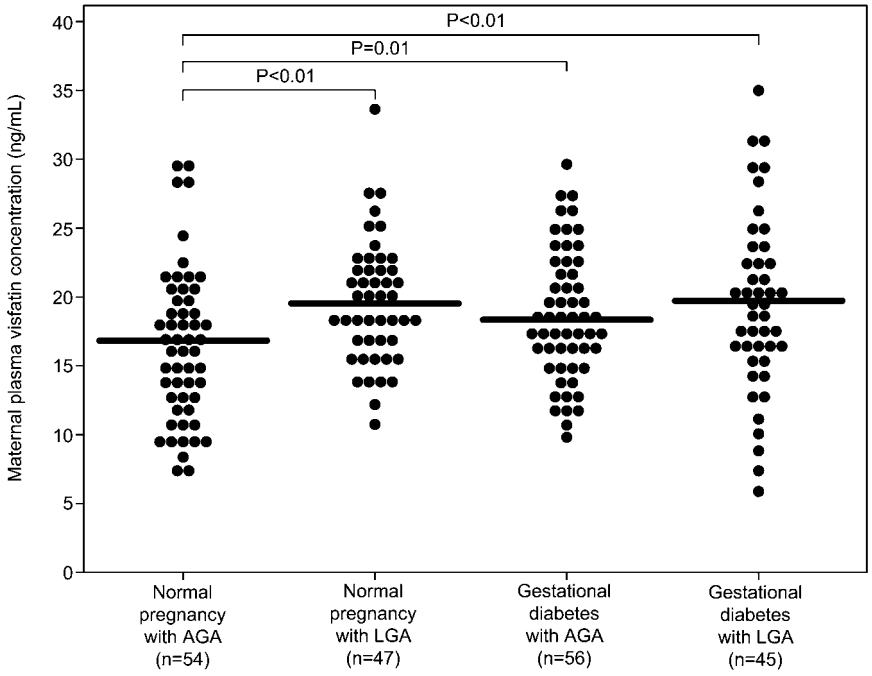

Figure 1 Comparison of the median maternal plasma visfatin concentrations between women with and without GDM and/or an LGA fetus.
The median maternal plasma visfatin concentration was higher in patients with GDM, either with an AGA or with LGA fetus, than that of those with a normal pregnancy and an AGA fetus. Likewise, pregnant women with a normal pregnancy and an LGA fetus had a higher median maternal plasma visfatin concentration than those with a normal pregnancy and an AGA fetus.

maternal plasma visfatin concentration than those with an AGA neonate (LGA: 18.8 ng/mL, IQR: 16.5–22.4 vs. normal AGA 13.7 ng/mL IQR 10.4–19.6, P = 0.003; Figure 2); however, such difference was not detected among women with a normal weight (P = 0.12).

Maternal plasma visfatin concentration in normal and overweight/obese pregnant women with gestational diabetes mellitus

Overweight/obese patients with GDM, either with an AGA (17.9 ng/mL, IQR: 15.4–22.3) or an LGA neonate (18.1 ng/mL, IQR: 15.0–22.4), had a higher median maternal plasma visfatin concentration than overweight/obese women with a normal pregnancy who delivered an AGA neonate (13.7 ng/mL, IQR 10.4–19.6; P = 0.01 and P = 0.03, respectively; Figure 2); however, such differences were not observed when normal weight patients with GDM, either with an AGA or an LGA neonate, were compared to normal weight women with a normal pregnancy and an LGA neonate (P = 0.96 and P = 0.29, respectively). In addition, among normal weight women with GDM, there was no significant difference in the median maternal plasma visfatin concentration between those who delivered an AGA and those who delivered an LGA neonate (P = 0.43).

In order to further study the association between maternal plasma visfatin concentration and possible confounding factors, a multiple linear regression analysis was performed. Gestational diabetes mellitus (P = 0.03) and the delivery of an LGA neonate (P = 0.008) were independently associated with higher maternal plasma visfatin concentrations after correction for first trimester maternal BMI, maternal age, and gestational age at blood collection (Table 2).

Discussion

Principal findings of the study

1) Among women who delivered an AGA neonate, the median maternal plasma concentration of visfatin was higher in patients with GDM than in those with a normal pregnancy; 2) among women with a normal pregnancy, those who delivered an LGA neonate had a higher median maternal plasma visfatin concentration than those who delivered an AGA neonate; 3) among patients with normal BMI, there were no significant differences in the median maternal plasma visfatin concentration between the four study groups; and 4) GDM, as well as delivery of an LGA neonate were independently associated with higher maternal plasma visfatin concentrations.

Visfatin is a novel adipokine with metabolic and immunoregulatory properties Visfatin, a highly con-

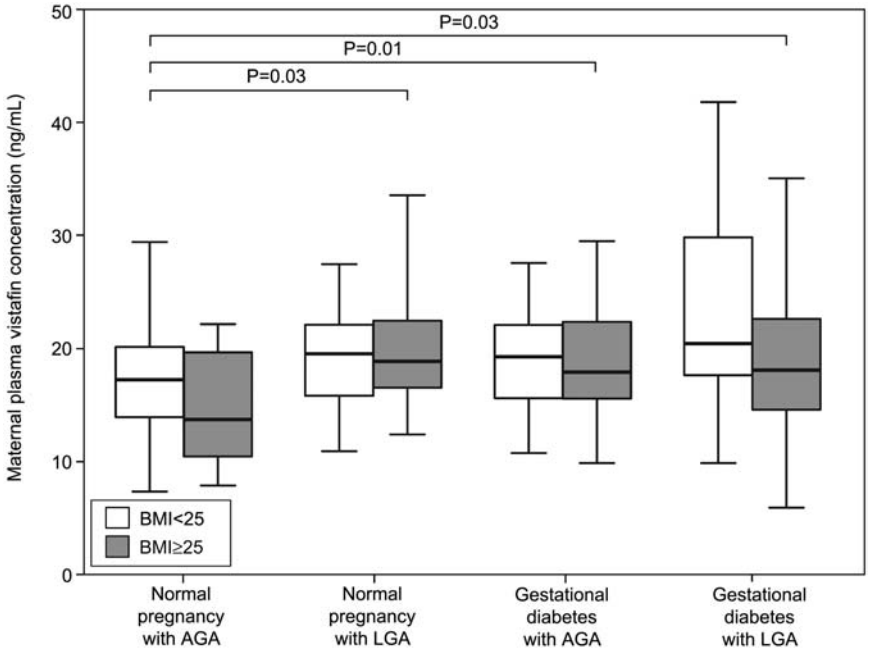

Figure 2 Comparison of the median maternal plasma visfatin concentrations between normal and overweight/obese pregnant women, with and without GDM and/or an LGA fetus.
Among overweight/obese patients, the median maternal plasma visfatin concentration was significantly higher in patients with GDM, either with an AGA or with LGA fetus, than that of those with a normal pregnancy and an AGA fetus. Likewise, overweight/obese pregnant women with a normal pregnancy and an LGA fetus had a higher median maternal plasma visfatin concentration than those with a normal pregnancy and an AGA fetus. In contrast, there was no significant difference in the median maternal plasma visfatin concentration among pregnant women with normal weight. Within each study group, the median maternal plasma visfatin concentration was comparable between normal and overweight/obese pregnant women.

Table 2 Linear regression analysis of factors associated with maternal plasma visfatin concentrations.

Factor	Beta	Significance
Delivery of LGA neonate	0.193	0.008
GDM	0.174	0.032
Maternal BMI	–0.120	0.115
Gestational age at blood collection	0.106	0.154
Maternal age	0.027	0.728

LGA, large for gestational age; GDM, gestational diabetes mellitus; BMI, body mass index.

served 52 kDa molecule, was originally cloned in 1994 from human peripheral blood lymphocytes [170], and its homologous proteins have been reported in bacteria [123], invertebrate [138], fish [61] and mammals [94, 124, 127, 142, 143, 148–151, 170, 198]. This adipokine enhances the effect of IL-7 and stem cell factor on pre-B-cell colony formation, hence it was named pre-B-cell enhancing factor (PBEF) [170]. Recently, visfatin/PBEF was reported to be produced by adipose tissue [19, 38, 60, 75, 173, 174], thus included in the growing family of adipokines. While preferentially produced by visceral fat depot [82, 174, 184], the expression of visfatin is not limited to adipose tissue. Indeed, it can be expressed in placenta, fetal membranes [95, 124, 142, 143, 148–151], myometrium [48], bone marrow, liver, muscle [170], heart, lung, kidney [170], macrophages [43], and neutrophils [86, 170, 198].

The physiologic role of visfatin in humans has not been fully elucidated; however, it has been proposed that this adipokine has a regulatory role in glucose metabolism and inflammation. The following features about visfatin suggest that this protein has a regulatory role in glucose homeostasis: 1) *in vitro*, adipocytes secrete visfatin in response to glucose exposure [73]; 2) administration of glucose to human subjects results in increase circulating visfatin concentration [73]; 3) obesity is associated with increased circulating visfatin concentration [19, 35, 55, 56, 72, 87, 171, 203], and plasma concentrations of this adipokine are positively correlated with BMI [19, 35, 113, 171] and waist-to-hip ratio [36]; 4) consistent with the aforementioned reports, serum concentration of visfatin in humans are positively correlated with the amount of intra-visceral fat as determined by computerized tomography scan [171]; 5) plasma concentrations of visfatin are higher in patients with type-2 DM [36, 53, 116, 171] or metabolic syndrome [55, 56] than in normal subjects; and 6) a visfatin promoter polymorphism is associated with a susceptibility to type-2 DM [204].

Evidence in support of the immunoregulatory effects of visfatin includes: 1) the production of proinflammatory

cytokines (e.g., IL-6, TNF-α, IL-1β) by human monocytes, is up-regulated by visfatin in a dose dependent manner [137]; 2) the expression of visfatin is increased following exposure to proinflammatory mediators such as TNF-α (in monocytes [43], macrophages [84] and neutrophils [86]), IL-6 (synovial [144] and amniotic epithelial cells [148]) and IL-8 and granulocyte/macrophage colony stimulating factor (in neutrophils [86]); 3) visfatin expression is increased in cells retrieved by bronchoalveolar lavage from patients with acute lung injury [198] and from lung tissue of animal models of acute lung injury [199]; similarly, its expression increases in neutrophils from septic patients [86]; 4) polymorphisms in the visfatin gene are associated with an increased *(–1001G)* or decreased *(–1543T)* risk of developing ARDS in septic shock patients than wild-type homozygotes [10]; and 5) patients with chronic inflammatory disorders such as inflammatory bowel disease [137] and rheumatoid arthritis [153] have higher circulating visfatin than normal subjects.

Adipose tissue dysfunction: a novel mechanism of disease for gestational diabetes mellitus Incapacity of the adipose tissue to meet the metabolic demands has been suggested as a putative mechanism of disease for type-2 DM [67, 106]. According to this hypothesis, one of the core components of adipose tissue failure is impaired production and/or secretion of adipokines. Indeed, several lines of evidence support a causality linkage between dysregulation of adipokines and type-2 DM: 1) mice deficient in adiponectin [103, 119, 140, 196], leptin [39, 80], or TNF-α [189] have insulin resistance; in addition, the administration of leptin [26, 74, 156], adiponectin [16, 59, 196] or neutralization of resistin [181] corrects insulin resistance in obese and diabetic mice; 2) polymorphisms at the locus of adiponectin [57, 70, 76, 81, 110, 132, 139, 182], resistin [131, 152], visfatin [204], or leptin receptor [168] are associated with insulin resistance and type-2 DM; and 3) patients with type-2 DM have a higher plasma concentrations of resistin [62, 129, 202], TNF-α [44, 135], RBP-4 [37, 197], CRP [54, 160] and a lower concentrations of adiponectin [79, 97, 160, 191], than normal subjects.

Gestational diabetes mellitus is defined as a carbohydrate intolerance of varying severity, with onset, or first recognition during pregnancy [1, 27, 64, 65, 134, 147]. This adverse metabolic state affects 1–10% of all pregnancies [4, 5, 14, 22, 27, 29, 45, 65, 66, 109, 147], and is associated with maternal, fetal and neonatal complications [5, 15, 17, 20, 23, 33, 40, 42, 45, 47, 85, 96, 100, 133, 141, 145, 146, 157, 172, 179, 180]. Similarly to type-2 DM, adipose tissue failure, characterized by altered maternal circulating concentration of adipokines (e.g., TNF-α [49, 78, 107, 154, 161, 186, 190, 201], CRP [128], leptin [9, 93, 99, 128] and adiponectin [9, 98, 162, 185, 192, 194]), has been implicated in the pathophysiology of GDM. Indeed, during pregnancy, maternal serum concentrations of several adipokines are correlated with clinical indices of insulin resistance (e.g., HOMA) [28, 99, 118, 128, 163]. Moreover, women with low circulating adiponectin concentrations [192] or high circulating concentrations of CRP [176, 193] during early pregnancy are more likely to develop GDM than those with normal concentrations of these adipokines. Collectively, these findings suggest that adipokines play a role in the pathophysiology of GDM.

Visfatin in human pregnancy There are only few reports regarding circulating visfatin concentrations in pregnant women [34, 50, 52, 71, 101, 112, 120, 121, 125]. Mastorakos et al. [125] conducted a longitudinal study in which maternal serum visfatin concentrations were determined in 80 normal pregnant women at 10–12, 24–26 and 34–36 weeks of gestation. During the first trimester, visfatin concentrations were negatively correlated with percentage of fat mass and hip circumference. However, during the second and third trimesters, serum concentrations of this adipokine were not correlated with these surrogate markers of adipose tissue quantity. The authors suggested that the progressive increase in insulin resistance with advancing gestation can be compensated by a sustained increase of visfatin secretion by the adipose tissue [125]. Fasshauer et al. [50] reported that during the third-trimester, women with intrauterine growth restriction (n = 18) had a higher mean maternal plasma visfatin concentration than those with an AGA neonate (n = 10). The same group reported that patients with preeclampsia in the third-trimester (n = 15) had a higher mean maternal serum visfatin concentration than normal pregnant women (n = 20) [52] and that maternal circulating visfatin was negatively correlated with HOMA-IR, but not with maternal age or BMI [52].

The association between maternal plasma visfatin concentrations and gestational diabetes mellitus We report herein that GDM is independently associated with increased maternal plasma visfatin concentrations. Studies regarding maternal circulating visfatin in patients with GDM are scant and inconsistent: both increased [101, 112] and decreased [34, 71] maternal visfatin concentrations were reported. Our findings are in agreement with those of Krzyanowska et al. [101] who reported a higher maternal circulating visfatin in 64 patients with GDM than in 30, mostly overweight, normal pregnant women at 28–30 weeks of gestation. Subsequently, Lewandowski et al. [112] reported higher maternal visfatin concentrations in 16 patients with GDM compared to 20 normal pregnant women at 28 weeks of gestation. In contrast, Chan et al. [34] demonstrated that patients with GDM (n = 20) in the late second trimester have a lower mean visfatin serum concentration than normal pregnant women (n = 20). Haider et al. [71] reported similar results in 10

patients with GDM and 10 aged-matched controls at the same gestational age (24–28 weeks). Differences in study design may contribute to explain the differences among studies. In particular, the number of subjects, gestational age at enrolment, differences in BMI and neonatal birth weights, differ between the studies.

The association between maternal plasma visfatin concentrations and neonatal birthweight The independent association between the delivery of an LGA neonate and elevated maternal plasma visfatin concentrations is a novel finding. Previous reports have underscored the association between fetal growth restriction (FGR) and increased maternal circulating visfatin. Fasshauer et al. [50] reported that mean plasma maternal visfatin in the third trimester is higher in patients with FGR than those with an AGA newborn. This finding was corroborated by Malamitsi-Puchner et al. [120]. Of interest, in the latter study, cord blood visfatin concentrations did not differ between SGA and AGA neonates [120]. The same group [121] reported that among patients with a normal pregnancy and an AGA neonate, the mean cord blood visfatin concentration was similar and positively correlated with the mean maternal visfatin concentration; furthermore, the mean cord blood visfatin concentration was positively correlated with neonatal birthweight. Based on these findings, the authors proposed that a passive transplacental transfer of visfatin is probable [120, 121]. López-Bermejo et al. [117] reported a negative association between cord blood visfatin concentrations and indices of fetal size only in mothers who smoked, indicating that cord blood visfatin concentrations may be, in part, under the regulation of maternal factors. Taken together, these findings suggest that visfatin has a role in the metabolic crosstalk between maternal and fetal compartments. The strong association reported herein, between the delivery of an LGA neonate and elevated maternal plasma visfatin concentrations in mothers with and without GDM further support this hypothesis.

Visfatin concentrations in GDM and LGA neonate: maternal metabolic status *vis-à-vis* neonatal birthweight Several explanations can account for the association of increased maternal plasma visfatin concentration and GDM or the delivery of an LGA neonate:

1. *Insulin resistance and impaired glucose metabolism in women with GDM and/or LGA neonate:* Insulin resistance is accompanied by increased visfatin production and/or secretion. Indeed, polymorphysms in the visfatin gene [204] are associated with insulin resistance and type-2 DM. *In vivo* clamp studies in humans demonstrated that hyperglycemia increases circulating visfatin concentrations [73]. Moreover, circulating visfatin concentrations in patients with type-2 DM are higher than in normal subjects [36, 53, 171]. Given the insulin-mimic effect of visfatin, it has been proposed that the increased concentrations of this hormone in the context of insulin resistance, reflect a compensatory mechanism aimed at ameliorating the functional consequences of insulin deficiency [116]. Collectively, these reports suggest an association between insulin resistance and elevated visfatin. This explanation can also be applicable, in part, to women with an LGA neonate and without GDM since minor abnormalities of glucose metabolism, even in the absence GDM, have been implicated in patients with neonatal overgrowth [92, 108, 111, 115, 130, 200].
2. *Overdistention of fetal membranes in patients with an LGA neonate: In vitro* studies have established a causality between stretching of human fetal membranes and increased expression, production, and secretion of visfatin [95, 142, 143, 149, 150]. Indeed, the visfatin gene is up-regulated in response to stretching of human fetal membranes [142, 143]. Moreover, visfatin has been shown to be secreted from amniotic epithelial-like cell line [150]. Recently, it has been demonstrated that both expression and secretion of visfatin increases after prolonged stretching of the fetal membranes [95]. Consistently, an increased immunostaining for visfatin was demonstrated in the amnion of twins and triplets [95]. Thus, it is tempting to speculate that the increased maternal plasma visfatin concentrations are derived, in part, from the stretched fetal membranes of women with LGA fetuses. In addition, expression of visfatin in human placenta have been reported [170]; thus, an increased secretion of visfatin from larger placentas of LGA fetuses can also account for our findings.

Collectively, transplacental transport, increased placental mass, and overdistation of fetal membranes may account for the increase in maternal plasma visfatin concentrations in pregnant women with an LGA neonate.

Disparity in circulating maternal visfatin between normal and overweight/obese pregnant women – the role of maternal metabolic state and neonatal weight As opposed to overweight/obese pregnant women, those with a normal BMI had a comparable median maternal visfatin concentration, regardless of their metabolic state (GDM) or neonatal birthweight. Consistent with our findings, Tsiotra et al. [188] reported that visfatin mRNA expression from human peripheral monocyte-enriched mononuclear cells is significantly elevated in type-2 diabetic women, compared to healthy control women, independently of the presence of overweight/obesity.

The association between circulating visfatin and overweight/obesity is still under debate. Several studies argued in favor of this association: serum visfatin concentration correlates with the amount of visceral fat depot [171], waist-to-hip ratio [36], and BMI [19, 35, 113,

171]. However, these reports were challenged by other investigators who failed to find a positive correlation between circulating visfatin and either visceral fat mass [19] or BMI [36, 46, 50, 53, 87, 102, 122, 175, 183, 203]. Currently, the exact physiologic and pathophysiologic role of visfatin is not fully elucidated, as reflected from this inconsistency in the literature. In the present study, first trimester BMI was not independently associated with maternal plasma visfatin concentrations after correction for confounding factors. Thus, a cause and effect relationship between BMI and maternal circulating visfatin concentrations data cannot be discerned. However, we were able to extend the abovementioned observations by demonstrating that the similarity between circulating maternal visfatin in normal and overweight women is unvaried even in the presence of GDM and/or LGA neonate.

Conclusion

The linkage between increased maternal circulating visfatin and the presence of GDM or delivery of an LGA neonate support the hypothesis that perturbation of adipokines homeostasis plays a role in the pathophysiology of GDM and excess fetal growth.

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